
Letter

Two recent publications in Cancer Research (1, 2) have stimulated us to write this letter to clarify the definition of the ACF. ACF were first defined and identified in 1987 (3) in rodents. The same definition permitted the identification of ACF in humans in 1991 (4). Subsequently, human ACF were shown to be monoclonal (5), i.e., the earliest identified neoplastic lesions in human colorectal cancers. Many laboratories have found in ACF altered genes and their products that are commonly observed in colon cancers (4, 6–12), and many laboratories are using ACF as biomarkers to assess the effects of colon carcinogens and chemopreventive agents (13–18). In studying the pathogenesis of other kinds of colonic lesions, it is important not to change the meaning of ACF as studied in a rapidly growing, published series of investigations from many laboratories.

Yamada et al. (1, 2) presented interesting data on β-catenin expression and mutations in early colonic lesions after the administration of azoxymethane to rats. The authors state that the lesions they have characterized, i.e., “β-catenin-accumulated crypts . . . are independent of ACF (aberrant crypt foci)” (Title, Abstract, Ref. 2). However, crypts that accumulate β-catenin in their cytoplasm and nuclei appear to us to be histologically indistinguishable from a subgroup of ACF that include most of the ACF with dysplasia.

ACF, by definition (3, 19), is identified microscopically in segments of unembedded colon. The use of the term “macroscopic” to describe these lesions in the title and throughout the first paper (1) ignores the definition of ACF and is misleading. In “Results,” Yamada et al. (1) state: “two populations of altered crypts were histologically detected.” The authors then equate one histological population with ACF and the second histological population with a new lesion without making clear how they related the histological preparations to the unembedded preparations where an ACF, by definition, is identified. The authors state (Discussion, Ref. 1) “an en face preparation technique is considered to provide a useful tool for the mapping and quantitation of mucosal aberration, including ACF (26).” We could not find anything about “en face preparations” in Ref. 26 by Suzui et al. En face preparations, as discussed by Hamilton et al. (25), are useful to identify histological alterations but do not identify or claim to identify an ACF that is first described 5 years after that publication. As illustrated in many publications (6, 11, 12, 19–22), an ACF can appear very different in histological sections, not unembedded colon, to identify lesions from carcinogen-treated rats for further study. The lesions that lack β-catenin expression in the cytoplasm are called ACF, and the lesions that accumulate β-catenin in the cytoplasm are called “lesions independent of aberrant crypt foci” (Title, Ref. 2). In “Results,” two reasons are provided for this designation: (a) “β-catenin-accumulated crypts did not present an ACF-like appearance in the whole-mount preparations . . . (Fig. 1)”; and (b) “The crypts often consisted of small crypts rather than enlarged crypts when compared with adjacent normal crypts.” The crypts illustrated (1, 2) with β-catenin expression in the cytoplasm are dysplastic and resemble the dysplastic ACF that we (6, 19, 23) and others have shown many times previously in both rodents (6, 19, 23) and humans (12, 20–22). Many of our ACF, including one with invasive cancer (6), were marked with ink in the unembedded tissue to be sure the pathology we saw in histological sections corresponded with ACF observed in unembedded tissue. Because dysplastic crypts show a marked loss of goblet cells they are smaller than some ACF with only mild atypia. Yamada et al. (Results, Ref. 2) state “ACF exhibited a monotonous histological appearance during the experiment, and the ACF score [histological abnormality] did not increase sequentially.” This is contrary to the reported histology of ACF in rodents and humans by many over a period of >10 years (6, 12, 17, 20–23). It appears that Yamada et al. have removed all the dysplastic ACF from the ACF category and placed them in a new category; this changes the fundamental nature of ACF and their role in colon carcinogenesis.

The final evidence (Fig. 6 in Ref. 2) that Yamada et al. present is an unembedded colon that shows two lesions lacking hexosaminidase activity. The authors (2) state that the top green lesion “does not have ACF-like appearance (normal-like crypts; open arrow);” however, our assessment is that it is an ACF. It is not as large as the other ACF in the field; but it satisfies the criteria that define ACF (i.e., as observed in an unembedded colon, the crypts are increased in size, have a thickened layer of epithelial cells, have increased pericryptal space, have irregular lumens, and are microscopically elevated). It does not meet the definition of enzyme-altered crypts that are morphologically normal (crypts with normal size and morphology) as we described them in 1993 (24).

In conclusion, the growing body of published investigations of ACF is based upon a definition of ACF that has not changed over more than a decade. The interpretation of these studies makes it important that the definition of ACF be consistent because other histological abnormalities may be described in the future.

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The abbreviation used is ACF, aberrant crypt focus.


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